# Solid-Phase Chemistry in the Total Synthesis of Non-Peptidic Natural Products

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**Abstract:** Solid-phase chemistry, first introduced for peptide synthesis in the 1960's, has become an integral part of organic synthetic methodology. Presented herein is an overview of recent examples of the use of solid-phase in the preparation of non-peptidic natural products and related compounds, encompassing on-resin total syntheses as well as the use of polymer-supported reagents in solution.

## INTRODUCTION

While the onset of combinatorial chemistry witnessed the synthesis of numerous heterocycles on solid-phase [1], it was not until the late 1990's that the feasibility of constructing highly complex molecules on solid support was demonstrated by several researchers. Solid-phase synthesis (SPS) is now the strategy of choice for the preparation of biomolecules such as peptides and oligonucleotides [2].

The total synthesis of a given compound on solid-phase is generally more complicated than the corresponding synthesis in solution. Low control of the reaction process, instability of the solid support under different conditions and under long synthetic strategies are few facts that frustrate this methodology from being general. The use of SPS for natural products has thus been applied primarily to the modification of core structures pre-assembled in solution. However, owing to the limited scope of this technique, total SPS strategies (*i.e.*, those carried out exclusively on solid-phase) are superior for cases in which structural diversity is paramount, such as the analoging of lead molecules in combinatorial programs.

This review is concerned with recent articles about the use of SPS in total syntheses and not SPS for minor structural modifications, a subject that has been discussed in previous reviews [3].

Several natural products and natural-product analogs have been totally synthesized on solid-phase. Furthermore, many solution-phase strategies used for the preparation of these types of compounds have incorporated resin-bound reagents for synthesis and/or purification. Examples of the aforementioned syntheses are provided and discussed herein.

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## (I) TOTAL SOLID-PHASE SYNTHESIS OF NON-PEPTIDIC NATURAL PRODUCTS

Epothilones are highly active compounds with an unusual mechanism of action, like taxol, they exhibit cytotoxicity to tumor cells by inducing microtubule assembly and stabilization. However, epothilones are effective against taxol-resistant cell lines [4].

The nine-step synthesis of Epothilone A reported by Nicolaou *et al.* [5], could be considered the first report of an elegant and convergent solid-phase synthesis of a complex natural product.

The strategy employed by the authors also allowed the preparation of a library of epothilone-like molecules [6]. The four key steps of the synthetic route were a Wittig reaction, an aldol condensation, an esterification and an interesting cyclization/cleavage metathesis reaction used to form the macrolactam system (Scheme **1**). Subsequent epoxidation in solution afforded epothilone A and its corresponding derivatives in good yields.

As shown in Scheme **1**, ylide resin **2** was prepared from a low-loading Merrifield resin and phosphonium salt intermediate **1**. The epothilone A analogs were obtained by modifying the three commercially unavailable building blocks used for the synthesis of the parent compound.

Demethoxyfumitremorgin C, a tetrahydro-β-carboline fused to a diketopiperazine ring, has been identified as a specific reversal agent for the breast cancer resistant protein (BCRP) transporter [7], and has also garnered much attention due to its capacity to arrest the cell cycle at the G2/M transition [8].

In 1999, Wang and Ganesan synthesized demethoxyfumitremorgin C and several analogs on solid-phase [9] based on previous work in solution [10], incorporating both peptide synthesis and the *N*-acyliminium Pictet-Spengler condensation. At the same time, van Loevezijn *et al.* used a similar strategy for the same target to generate a library of 42 members [11]. Due to the similarity of the two aforementioned strategies, only that of Ganesan, *et al.*, will be discussed herein.

Commercially available Fmoc-L-Trp immobilized on polystyrene-Wang resin was first transformed into imine **17**

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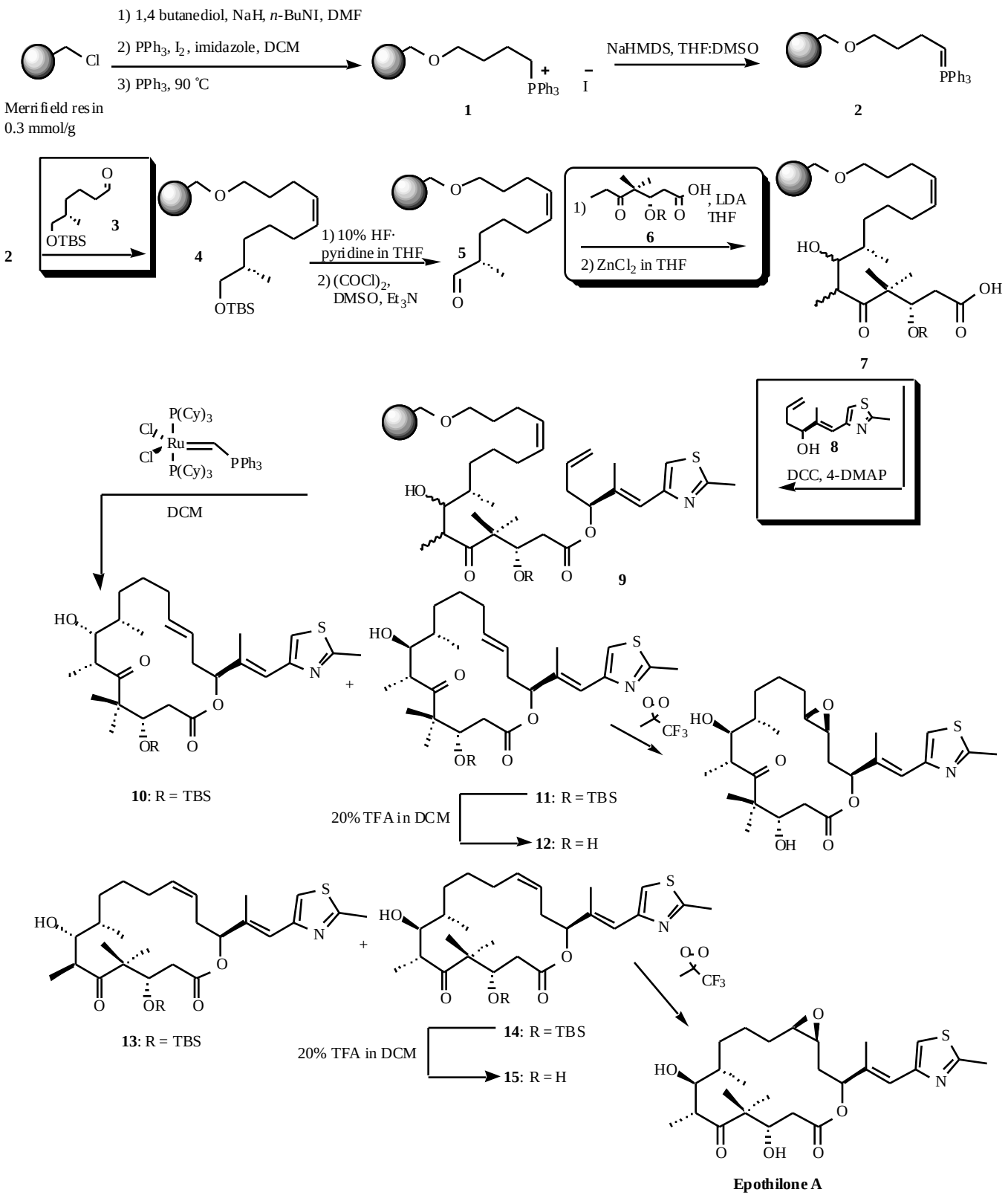
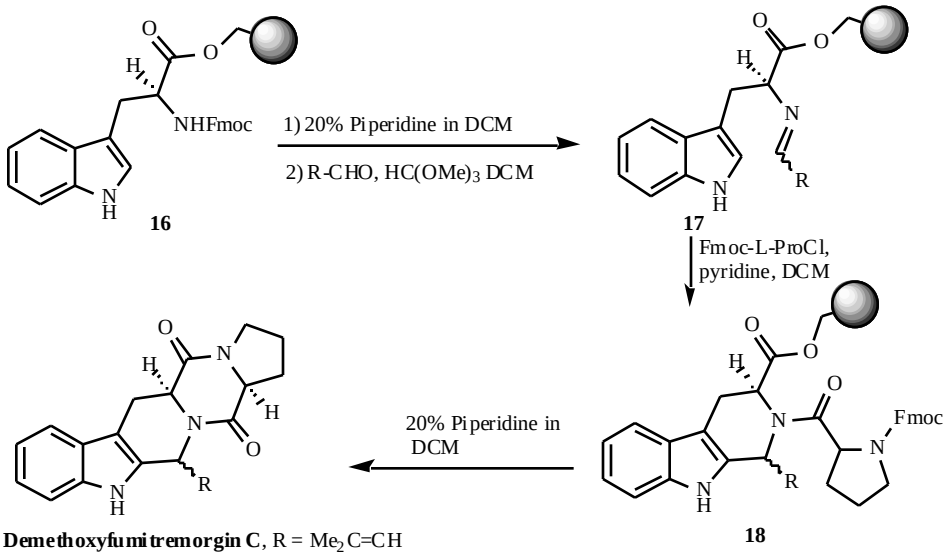


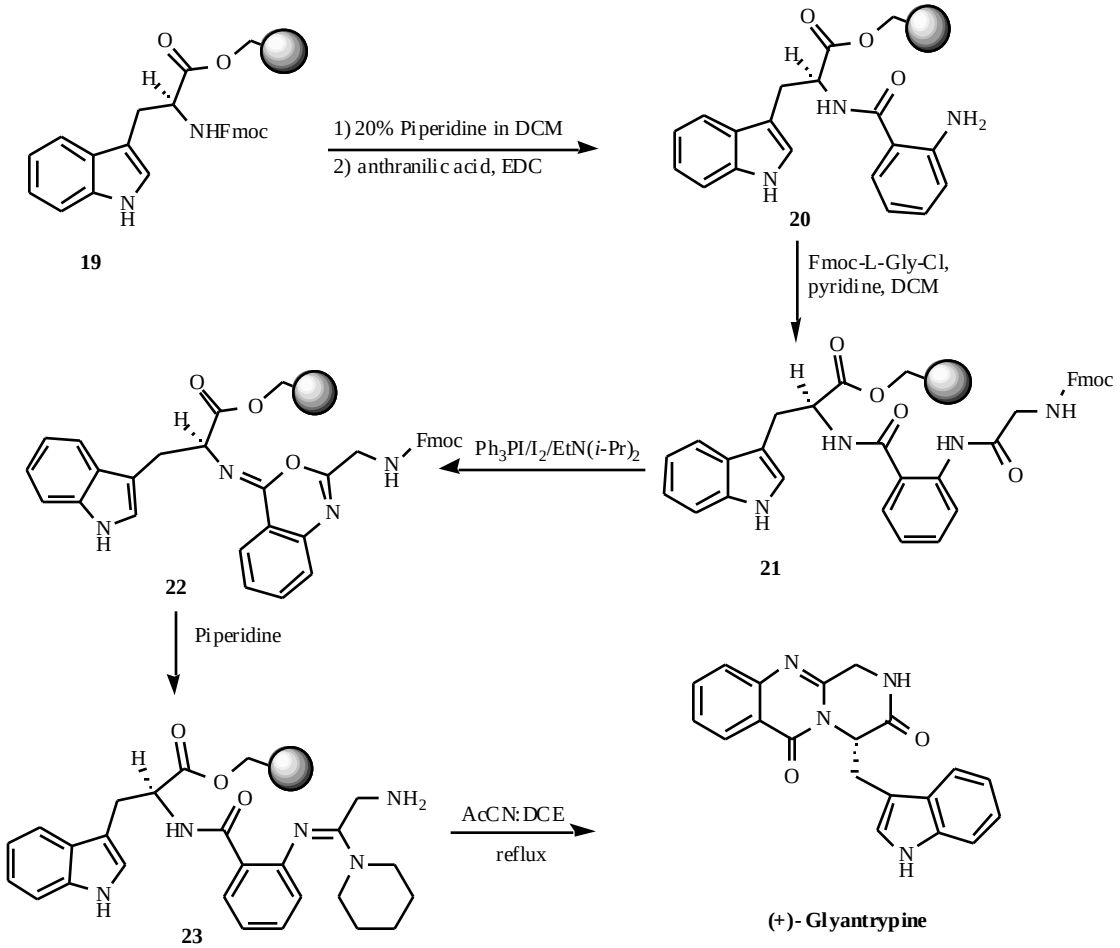

**Scheme 1.**

(Scheme **2**). Treatment of **17** with Fmoc-L-Pro acid chloride induced an *N*-acyliminium Pictet-Spengler reaction. Subsequent elimination of the Fmoc led to clean cleavage of the peptide-resin bond *via* diketopiperazine ring formation, yielding demethoxyfumitremorgin C. This reaction was not stereospecific, affording a mixture of *cis* and *trans* products (53:47, respectively). An increase in stereospecificity was detected during library preparation when different substituents were used. Thus, the *trans* isomer was the major product when bulky groups were used.




**Scheme 2.**

Inspired by their previous work in solution [12], Wang and Ganesan prepared (+)-glyantrypine and several fumiquinazoline alkaloids [13]. The total SPS involved two peptide coupling steps and started from commercially available Fmoc-L-Trp-functionalized Wang resin (Scheme **3**), on which Trp was replaced with other amino acids for the library production. The Fmoc group was removed and the amine was coupled to anthranilic acid. The second step was acylation of the aniline with Fmoc-Gly-Cl, followed by a dehydrative cyclization of linear tripeptide **21**. Piperidine-mediated removal of the Fmoc group and subsequent rearrangement of oxazine **22** led to amidine carboxamide **23**, which was then refluxed in ACN to induce the cyclative cleavage of (+)-glyantrypine from the resin.




**Scheme 3.**

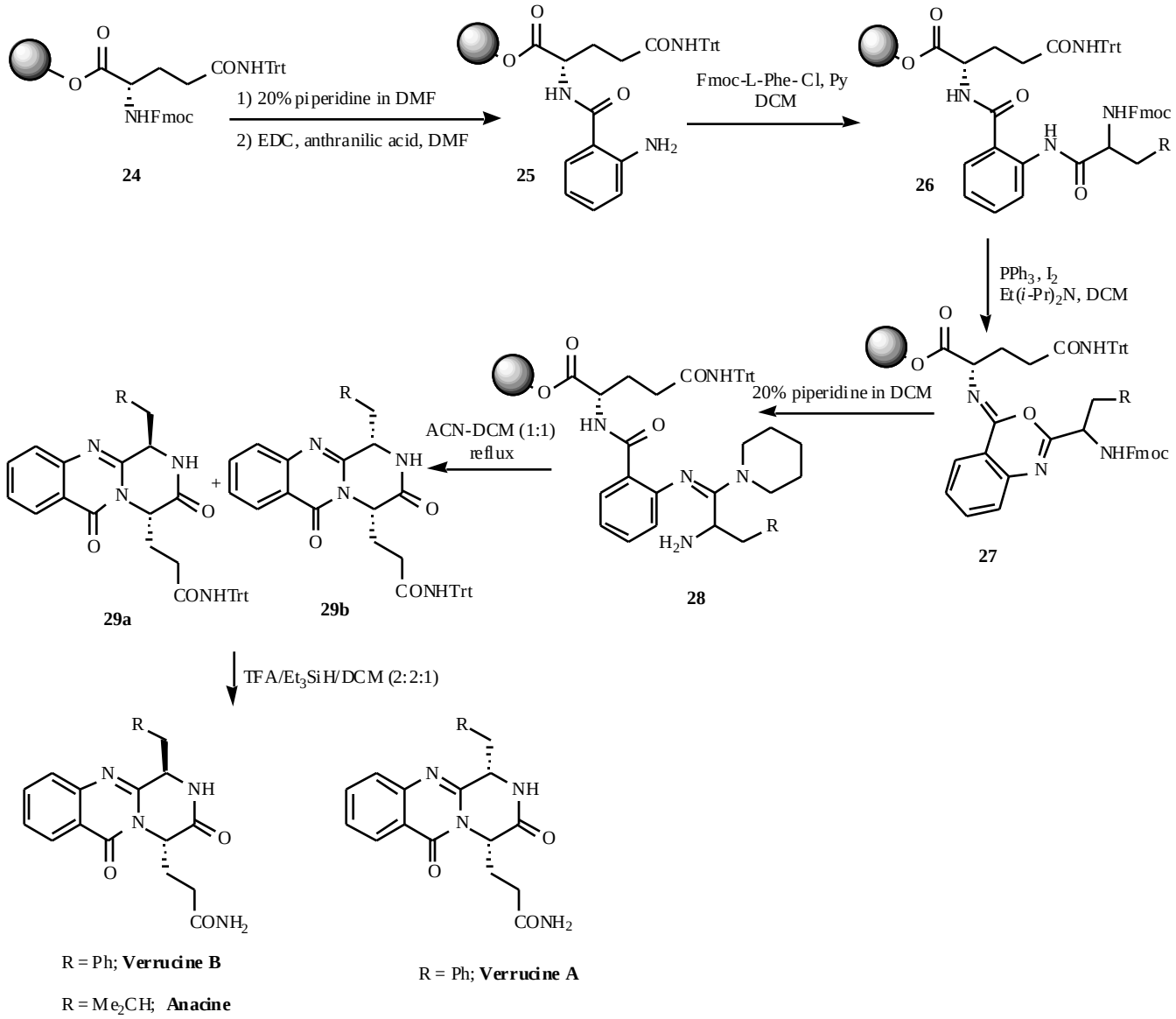
In 2001 Wang and Sim adapted an earlier protocol [13] to perform the first total solid-phase syntheses of verrucines A and B as well as anacine using a Sasrin resin [14].

Starting with Fmoc-L-Gln(Trt)-Sasrin-resin **24**, (Scheme **4**) the deprotected amino resin was coupled to anthranilic acid to give peptide **25**. The anthranilamide was then acylated with Fmoc-L-Phe-Cl. The linear peptide **26** was dehydrated to give benzoxazine **27**, which was further deprotected and transformed to the amidine intermediate **28**. Cyclization of **28** in refluxing ACN-DCM provided *N*-trityl verrucine A (**29b**). (+)-Verrucine A was obtained by deprotection with TFA-$Et_3SiH$-DCM (2:2:1). (+)-Verrucine B and (+)-anacine were obtained in a similar manner using Fmoc-D-Phe-Cl and Fmoc-L-Leu-Cl, respectively.

Although the yields obtained were relatively low, the purity of the final compounds was high, as only the desired cyclized compounds were released from the resin.

Lamellarins have exhibited great pharmacological potential, including antitumor and anti-HIV-1 activities, multi-drug resistance (MDR) reversal, and immunomodulation [15]. The first total SPS of the pentacyclic systems lamellarin U and L were recently reported [16].

Hydroxymethyl polystyrene or Wang resin-bound 2-methoxy-5-iodophenol **31** was coupled with an arylacetylene under Sonogashira cross-coupling conditions. A Bayer-Villiger reaction followed by a hydrolysis were used in the key transformation of the benzaldehyde into the corresponding phenol group. Ester bond formation under classical conditions gave **35**, which in turn was *N*-alkylated with 3,4-dihydro-6,7-dimethoxyisoquinoline. Subsequent [3+2] cycloaddition provided the pentacyclic system, which was cleaved using acidic conditions to yield different lamellarins according to the cleavage reagents used [17]. Thus hydroxy lamellarin derivatives were obtained when $AlCl_3$ or $SnCl_4$ were used, while use of $ZnBr_2$ and AcBr led to the desired diacetyllamellarins. Finally, cleavage of the Wang resin **37** with TFA-DCM (1:1) gave the corresponding 3-*O*-isopropyllamellarin U. This allowed the introduction of




**Scheme 4.**

three different building blocks, suggesting great versatility for future developments in combinatorial chemistry (Scheme **5**).

## (II) TOTAL SOLID-PHASE SYNTHESIS OF NATURAL PRODUCT ANALOGS

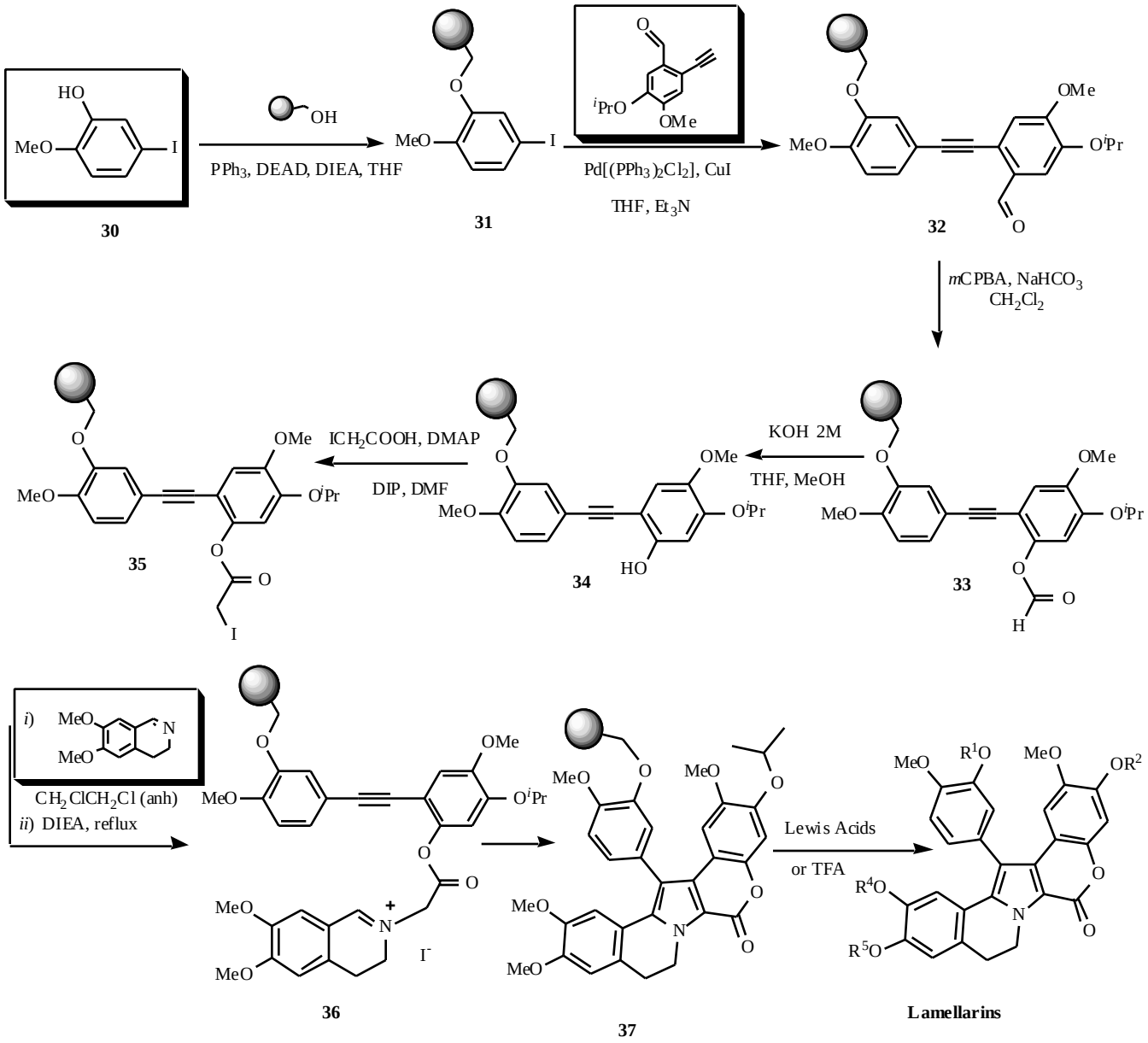
Myers *et. al*. have described a successful adaptation of their prior work in solution [18] to obtain structurally complex saframycin analogs by a ten-step solid supported synthesis with excellent yields (Scheme **6**) [19].

Attachment of the *anti*-morpholino nitrile to the solid support was achieved by silyl ether formation with 4-(chlorodiisopropylsilyl)polystyrene. Selective deprotection of the *t*-butyldimethylsilyl ether group of the resin-bound intermediate **38** followed by Fmoc elimination provided the amino phenol **39**. Addition of the *N*-protected α-amino aldehyde **40** to the amino-terminal intermediate provided the corresponding resin-supported imine.

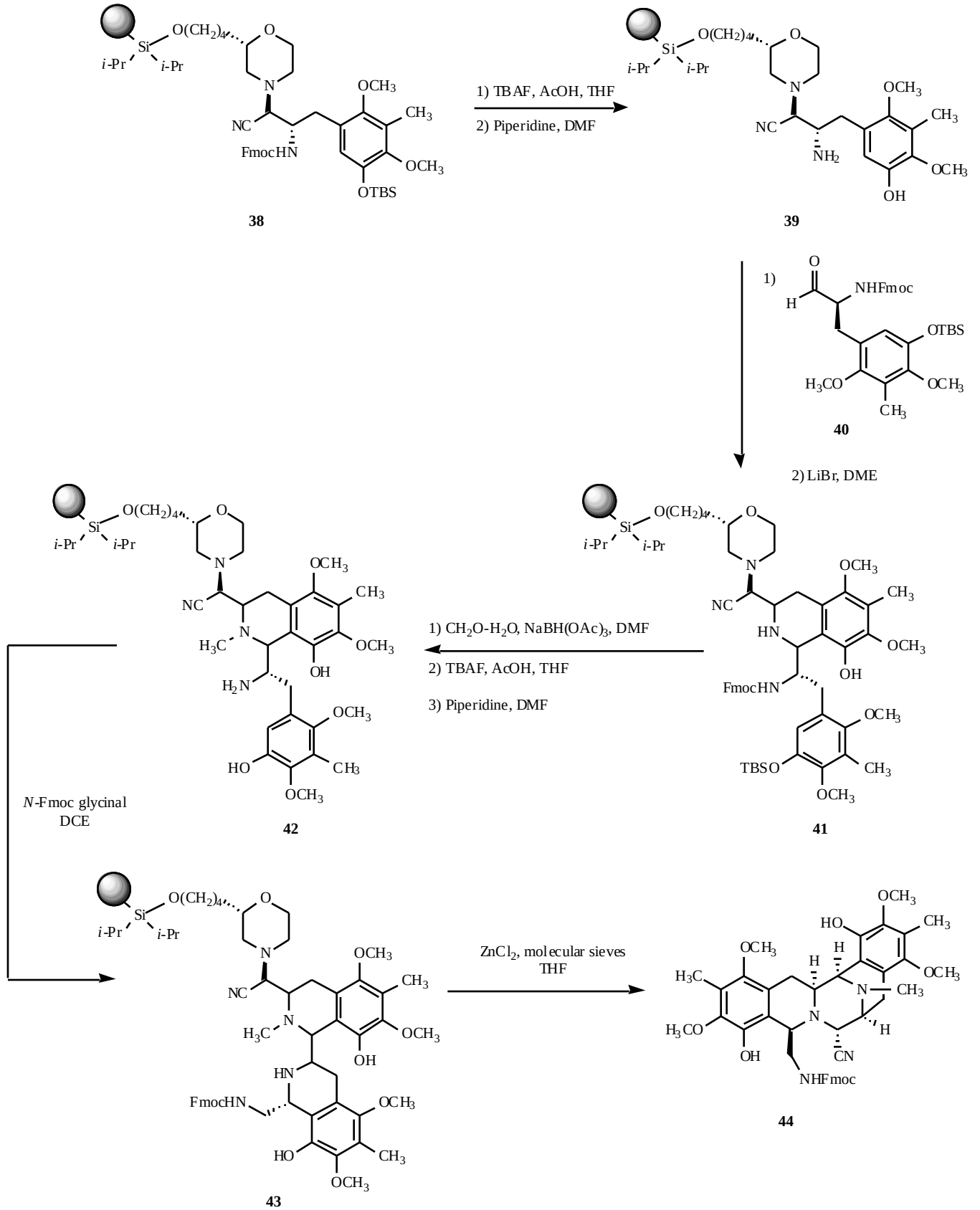
Further heating of the intermediate in a saturated solution of anhydrous LiBr in DME induced a Pictet-Spengler cyclization reaction, affording the *cis*-tetrahydroisoquinoline derivative **41** in good stereoselectivity. This is a good example of the utility of dual linkers in SPS.

Cyclization and subsequent auto-release were accomplished in one step *via* heating in the presence of $ZnCl_2$ to provide the saframycin analog **44** in excellent yields. A key feature of this strategy is its diastereospecificity, due to the fact that only one diastereomer is capable of cyclization and, consequently, detachment from the resin.

Prostaglandins, which possess a wide range of important biological activities [20], have been synthesized on solid-phase by Ellman, *et. al*. [21]. The strategy utilized by the authors allowed access to series 1 and 2 prostaglandins as either E or F derivatives.




**Scheme 5.**




**Scheme 6.**

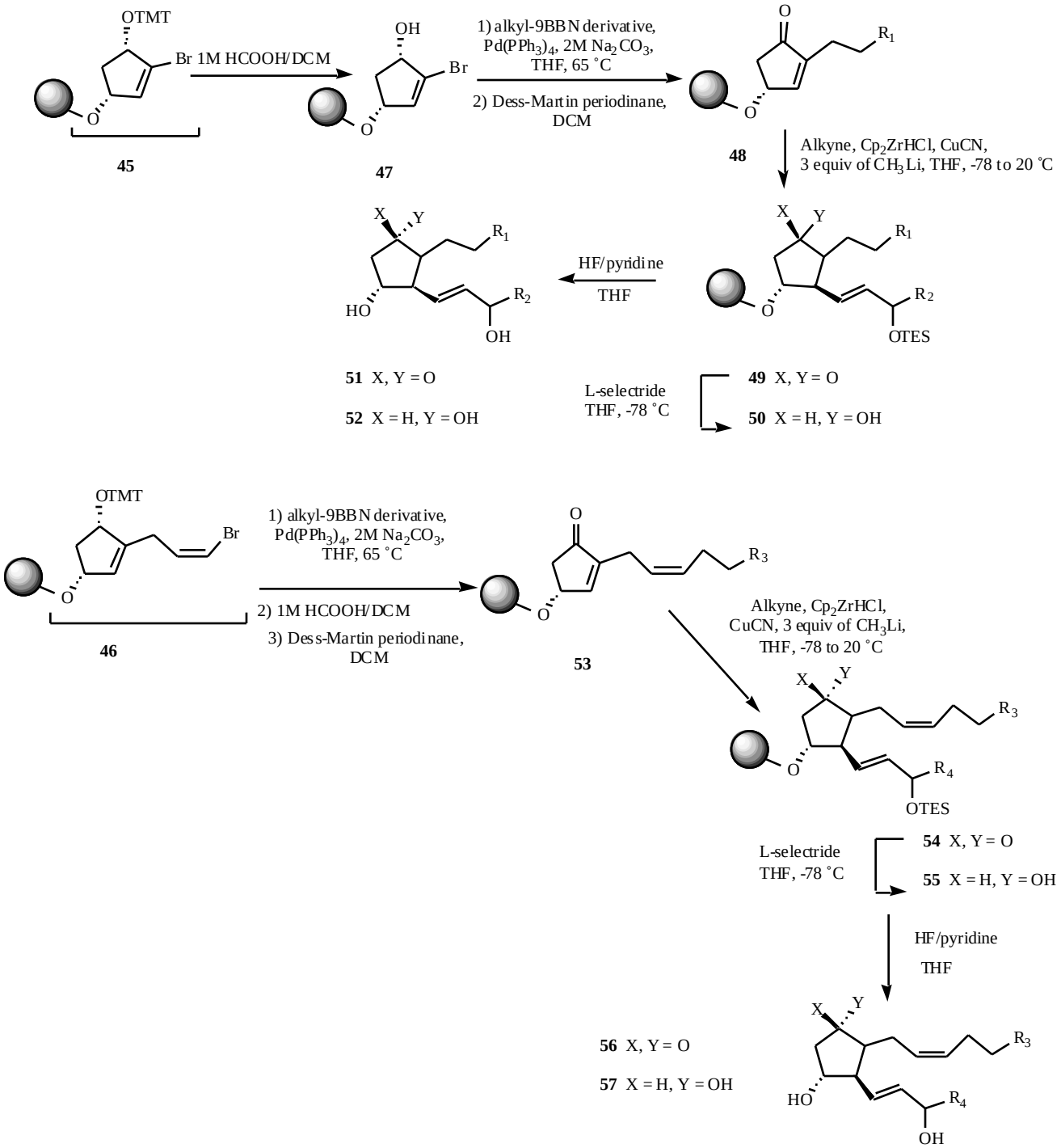
Two different cyclopentane cores that had been previously synthesized in solution provided access to prostaglandin derivatives of series 1 (**45**) and series 2 (**46**), illustrated in Scheme **7**.

In contrast with the use of diisopropylsilyl chloride resin, which does not cleave readily in dilute HF/pyridine, the use of a dibutylsilyl chloride resin and trimethoxytrityl (TMT) protecting group led to the prostaglandin systems.

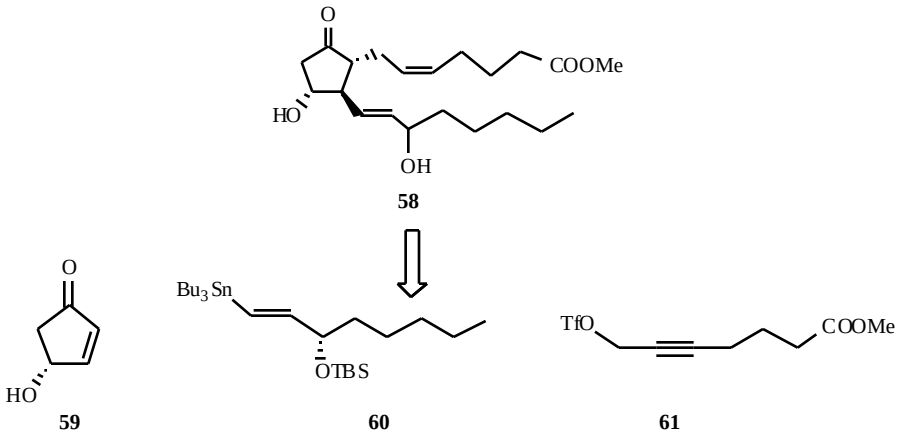
Diversity was introduced mainly in two steps: a Suzuki cross-coupling reaction and, at the lower side chain, the addition of vinyl cuprates prepared *in situ* by hydrozirconation of terminal alkynes followed by transmetalation [22]. Both prostaglandin series were synthesized in good yields and in high diastereomeric purity.

A set of 26 prostaglandins were synthesized in parallel by Ellman, *et al*. using the same methodology [23].

Using a soluble-polymer support, Janda, *et al*. synthesized the prostaglandin $E_2$ methyl ester **58** in high yield and purity (Scheme **8**) [24]. The key reagents used were a soluble, non-cross-linked chloromethylated polystyrene (NCPS) resin, previously used for peptide synthesis [25] and custom-modified (3,4-dihydro-2H-pyran-2-yl-methoxymethyl polystyrene) as well as three different pre-fabricated building blocks: the cyclopenten-1-one **59**, the vinylstannane ω-chain **60** and a triflate z-chain fragment **61**.




**Scheme 7.**

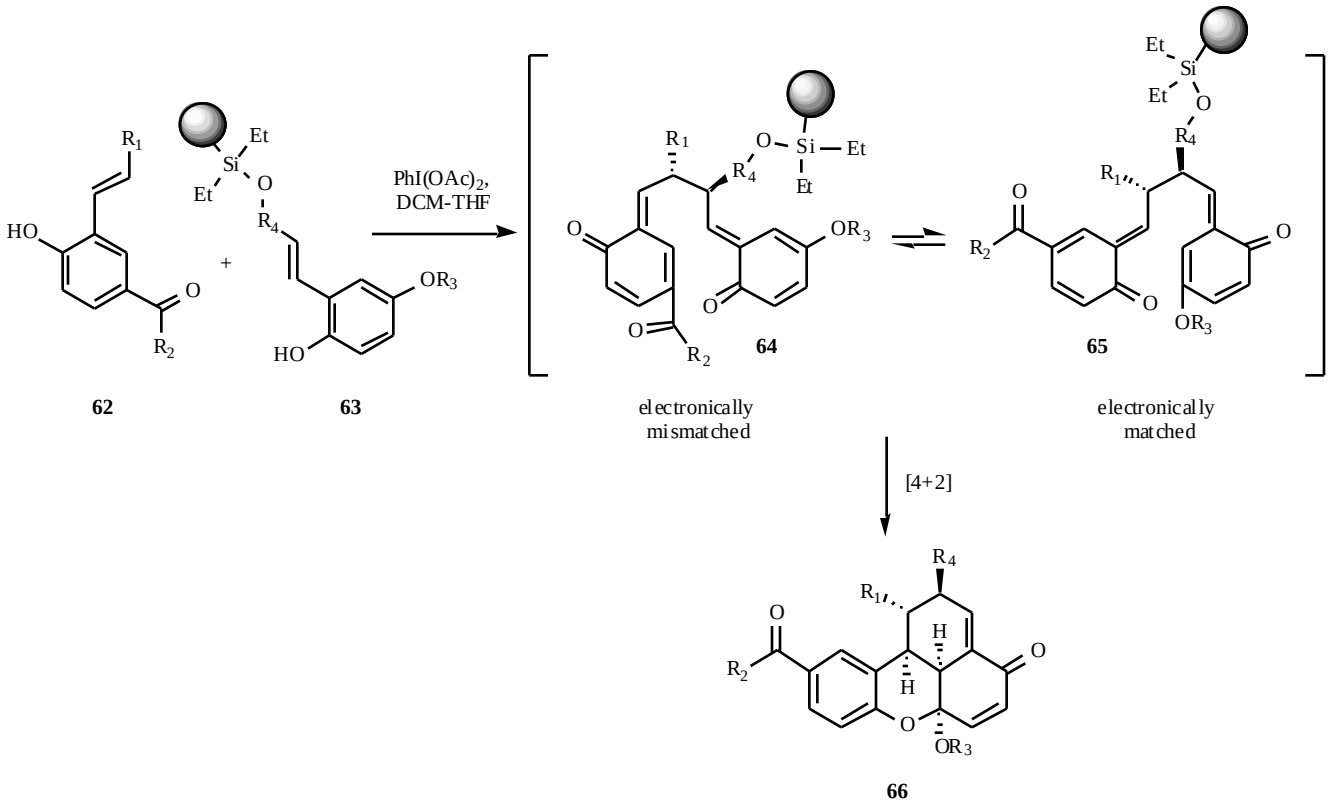



**Scheme 8.**

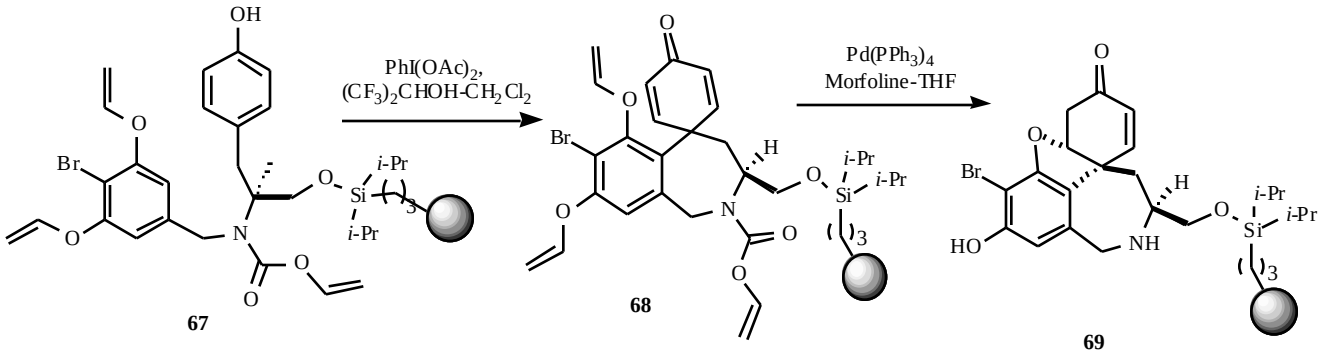
This work exemplified the use of a NCPS resin in place of a PEG-based support for combinatorial chemistry [26].

An elegant approach to the synthesis of carpanone was developed by Chapman via a biomimetic pathway based on a diastereoselective oxidative homocoupling followed by endo-selective inverse electron demand Diels–Alder cycloaddition [27]. Shair, *et al.*, inspired by Chapman's work, recently developed a solid-phase biomimetic strategy for the one-step construction of a tetracycle [28]. The key factor was the use of electronically differentiated *o*-hydroxystyrenes. Under the influence of the oxidant $PhI(OAc)_2$, the less reactive electron-deficient phenol **62** reacts with the more reactive electron-rich phenol **63** immobilized on the solid-phase (Scheme **9**). Following oxidative heterocoupling, an inverse electron demand Diels-Alder reaction gives the more electronically stable tetracycle **66**. This outstanding strategy afforded the tetracyclic molecules with control over five stereocenters and four initial positions of diversity. The authors explored the generality of the solid-phase reaction for diversity-oriented synthesis [29]. In each case, the tetracyclic adducts were obtained as single isomers resulting from complete electronic control during the inverse electron demand Diels-Alder cycloadditions.

Combinatorial libraries based on natural products have primarily been synthesized for drug discovery to provide analogs with improved activity and/or pharmacokinetics with respect to the parent compound. However, diversity-oriented libraries are used in the same field to generate structural analogs with biological activities different than

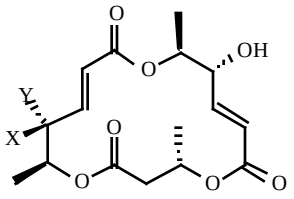



**Scheme 9.**




**Scheme 10.**

those of the natural product. Shair, *et al*. synthesized a library of 2946 galanthamine-like compounds (of which 2527 were confirmed) [30] using a biomimetic strategy in which a tyrosine derivative was attached to high capacity polystyrene beads through a Si-O bond. The key step was the exposure of **67** to $PhI(OAc)_2$ to afford **68,** which in turn converted to **69** via Pd-mediated deprotection and spontaneous cyclization (Scheme **10**). Further modifications of the main core **69** yielded several galanthamine-like derivatives.



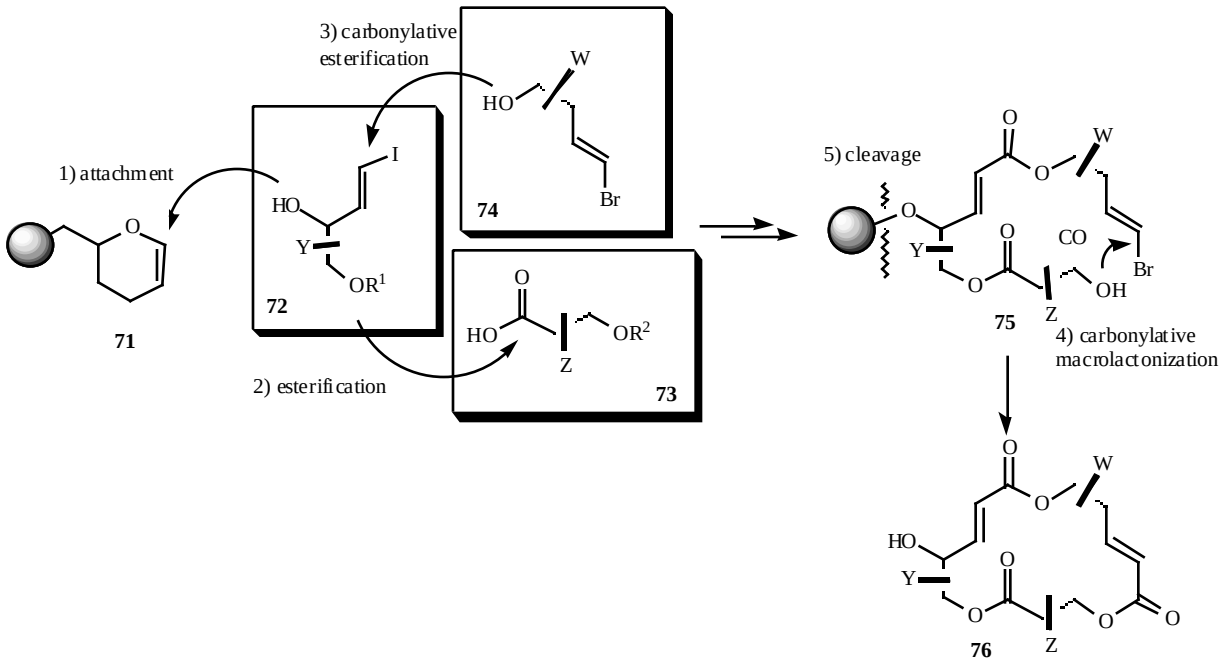
**Macrosphelide A**: X = H, Y = OH
**Macrosphelide B**: X = Y = O

**Fig. (1).**

Recently, Takahashi, *et al*. have developed an unprecedented solid phase macrolactonization for the synthesis of macrosphelide analogs [31]. Macrosphelides A and B (Fig. **1**) [32] strongly inhibit the adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVEC) in a dose-dependent fashion [33]. The authors described a highly convergent SPS of macrosphelide analogs in which palladium-catalyzed chemoselective carbonylation of vinyl halides was applied.

The synthesis began with attachment of a secondary alcohol in building block **72** to a dihydropyran-polystyrene (DHP-PS) resin and subsequent esterification with the building block **73**. Chemoselective carbonylation [34] of the vinyl iodide of **72** with the vinyl bromide-containing alcohol **74** was followed by carbonylative macrolactonization [35] of polymer-supported **75,** exploiting the less reactive vinyl bromide unit. The final step was cleavage of the product from the polymer-support (Scheme **11**).

This approach enabled the preparation of a 122-member macrosphelide library, including macrosphelides A, C, E, and F [31].




**Scheme 11.**

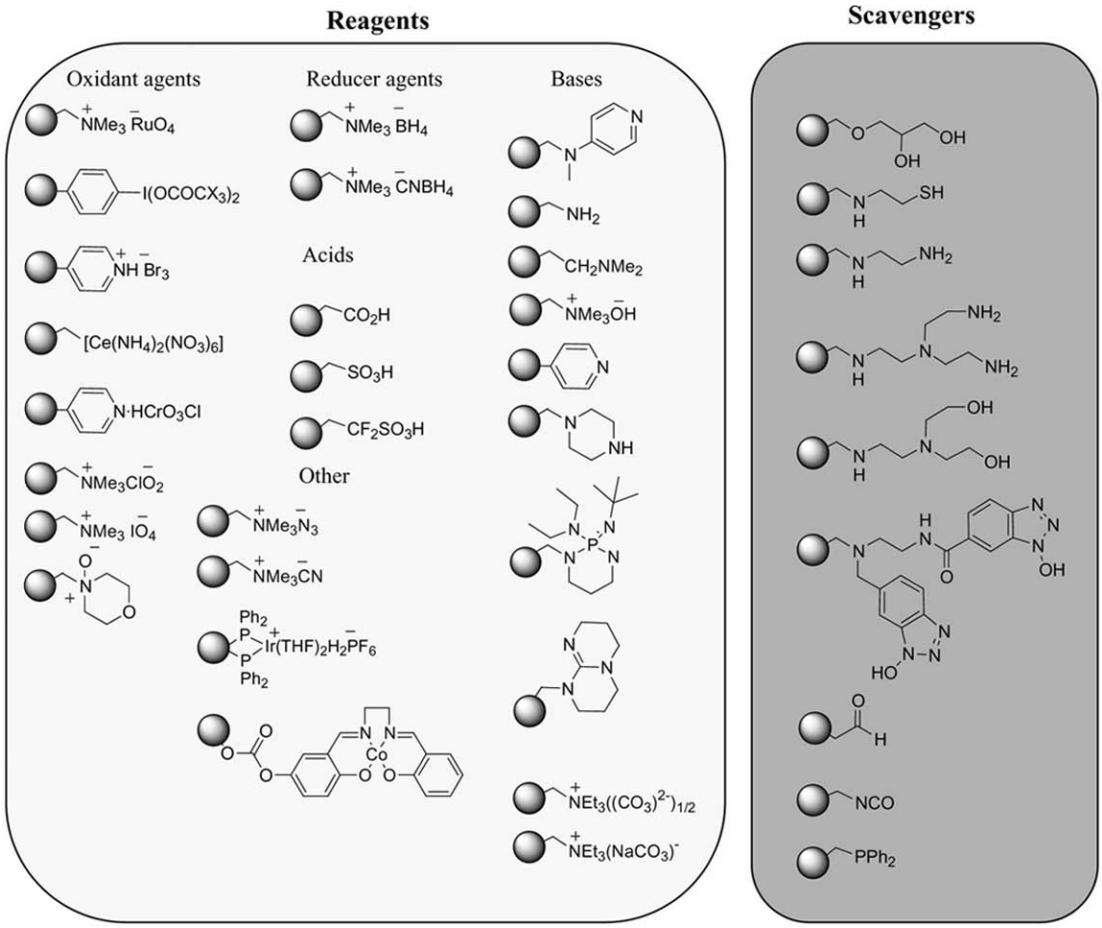

Reagents
Scavengers
Oxidant agents
Reducer agents
Bases
Acids
Other

**Fig. (2).**

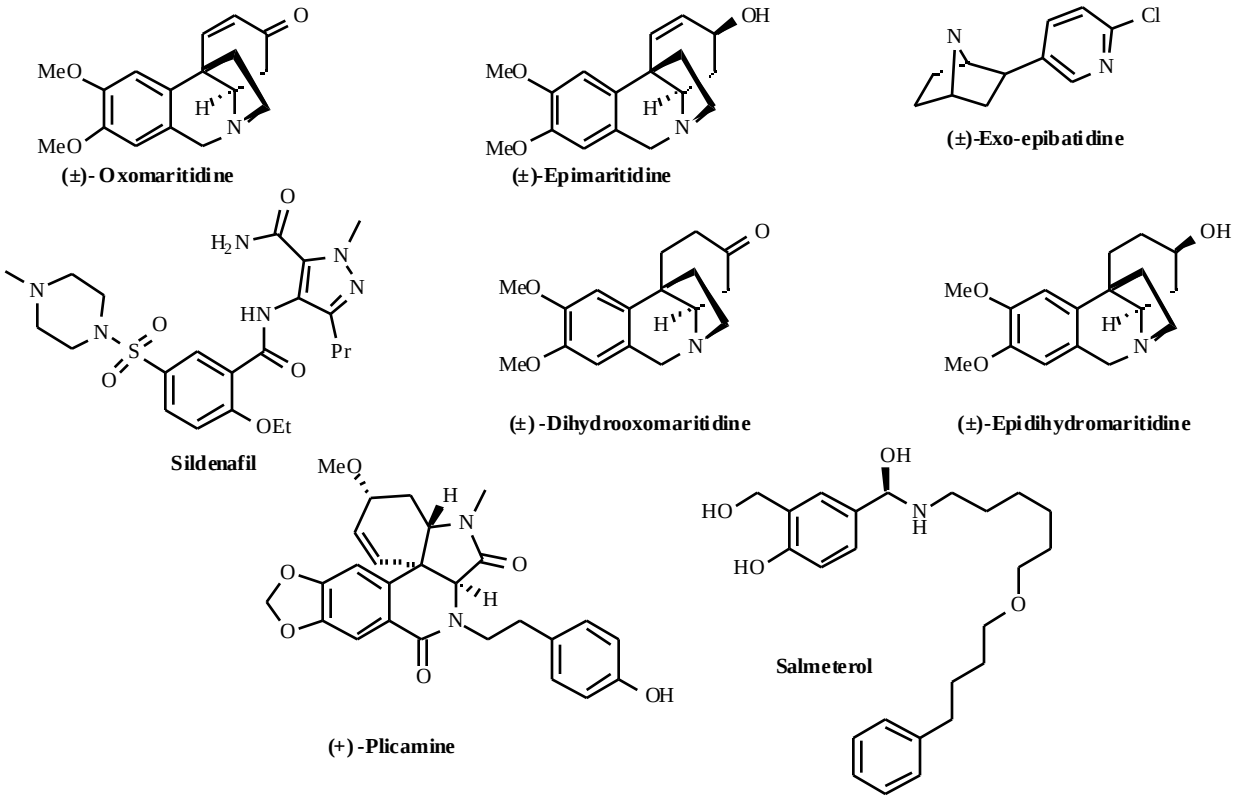
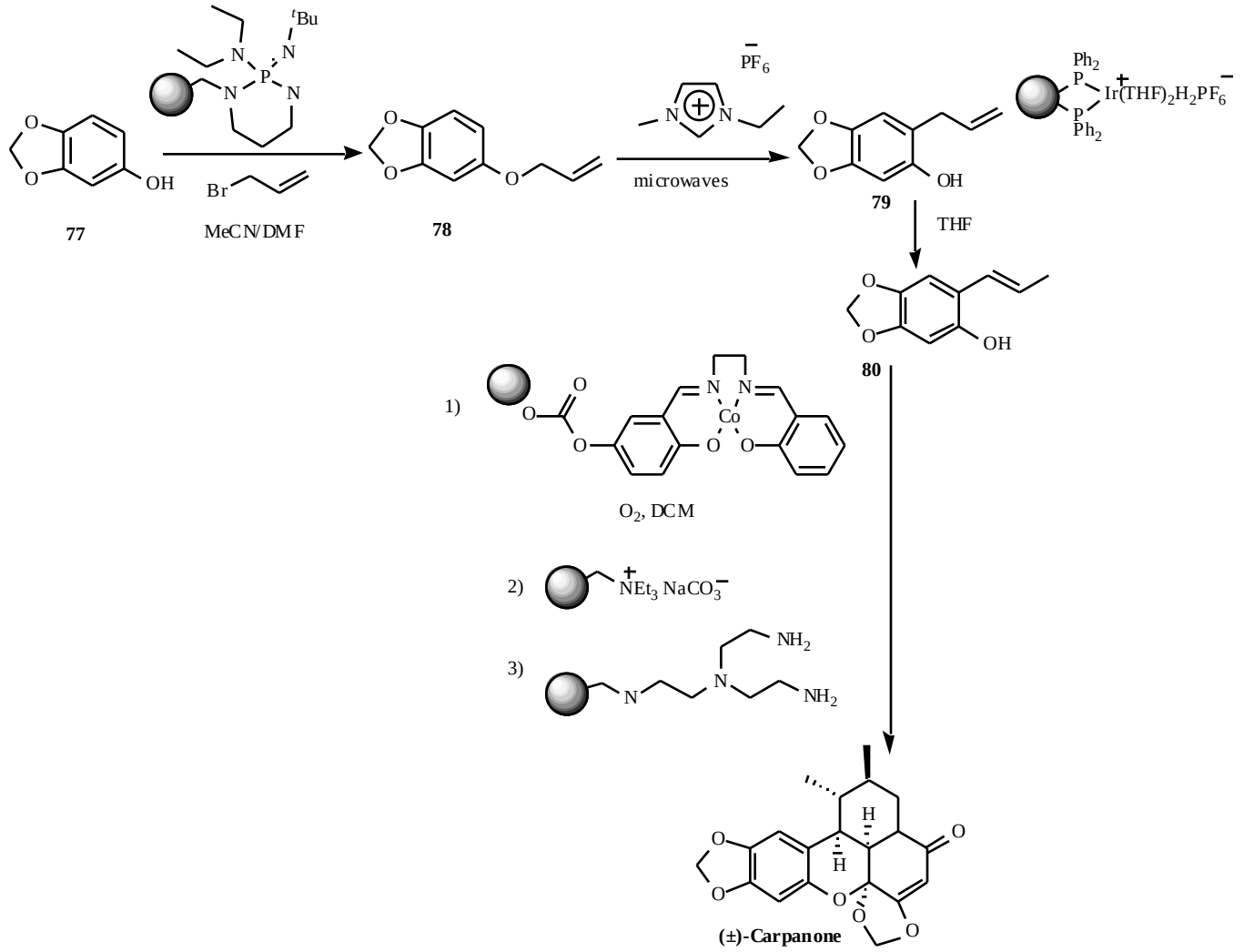

(±)- Oxomaritidine
(±)-Epimaritidine
(±)-Exo-epibatidine
Sildenafil
(±)-Dihydrooxomaritidine
(±)-Epidihydromaritidine
(+)-Plicamine
Salmeterol

**Fig. (3).**




**Scheme 12.**

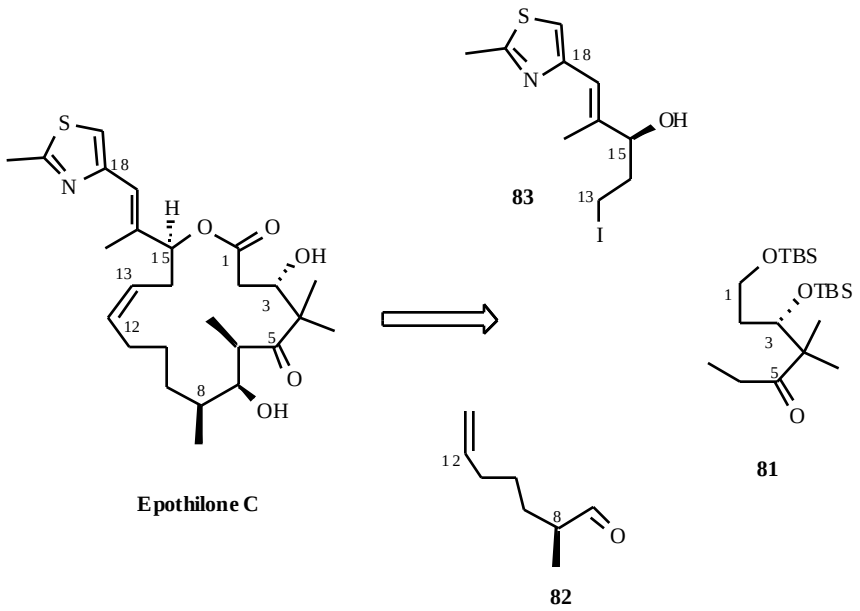
## (III) TOTAL SYNTHESES INCORPORATING SOLID-SUPPORTED REAGENTS AND SCAVENGERS

On the contrary to the dogma of preparing compounds libraries on solid support, and taken advantage of the combination of solution with solid-phase Ley *et al.* achieved the first total syntheses of natural products using a sequence of polymer supported reagents and scavengers (Fig. **2**).

As proof-of-principle, the authors prepared the alkaloids (±)-oxomaritidine and (±)-epimaritidine [36] and the potent analgesic compound (±)-epibatidine in a ten step sequence [37]. They went on to demonstrate the power of this methodology with the synthesis of sildenafil [38] (commercially known as Viagra™), the most widely sold globally marketed prescription drug, as well as the first total synthesis of the complex alkaloid (+)-plicamine and its enantiomer [39]. Successful preparation of the $\beta_2$ agonist (R)-salmeterol [40], nornicotine, nicotine, and a small library of further functionalized derivatives represented a significant advancement for SPS methodology (Fig. **3**) [41]. By introducing a chiral amine auxiliary into the original strategy to control the stereochemistry of the reaction, the authors were able to selectively obtain both enantiomers of nicotine [41].

During the SPS of carpanone [42], Ley, *et al.*, developed new polymer supported reagents [43]. The route to carpanone began with commercially available sesamol (**77**) which was allylated using allyl bromide and a polymer-supported phosphazene base to give the aryl ether **78** (Scheme **12**). A Claisen-type rearrangement was performed using a toluene-ionic liquid (1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate) biphasic system and heating in a focused microwave well system with excellent conversion. A key step was the isomerization of **79**, which had to be studied under different conditions. A solid supported version of Felkin's iridium catalyst was developed to afford the desired *trans* product in an excellent *trans-cis* ratio (127:1). The last step was also explored thoroughly, and it was ultimately found that a polymer-supported version of Co(salen) catalyst provided (±)-carpanone in high yield and purity.

The total synthesis of epothilone can be considered as a breakthrough in the field of solid-supported reagents and scavengers. Ley and co-workers [44], demonstrated the scope and utility of resin-bound reagents and scavenging




**Scheme 13.**

techniques for multi-step synthesis by stereoselectively synthesizing epothilone C.

Combining well-established chemistry with new solid-supported reagents and techniques, the authors developed a route in which the diastereoselective coupling of the three fragments **81**, **82** and **83** provides epothilone C (Scheme **13**).

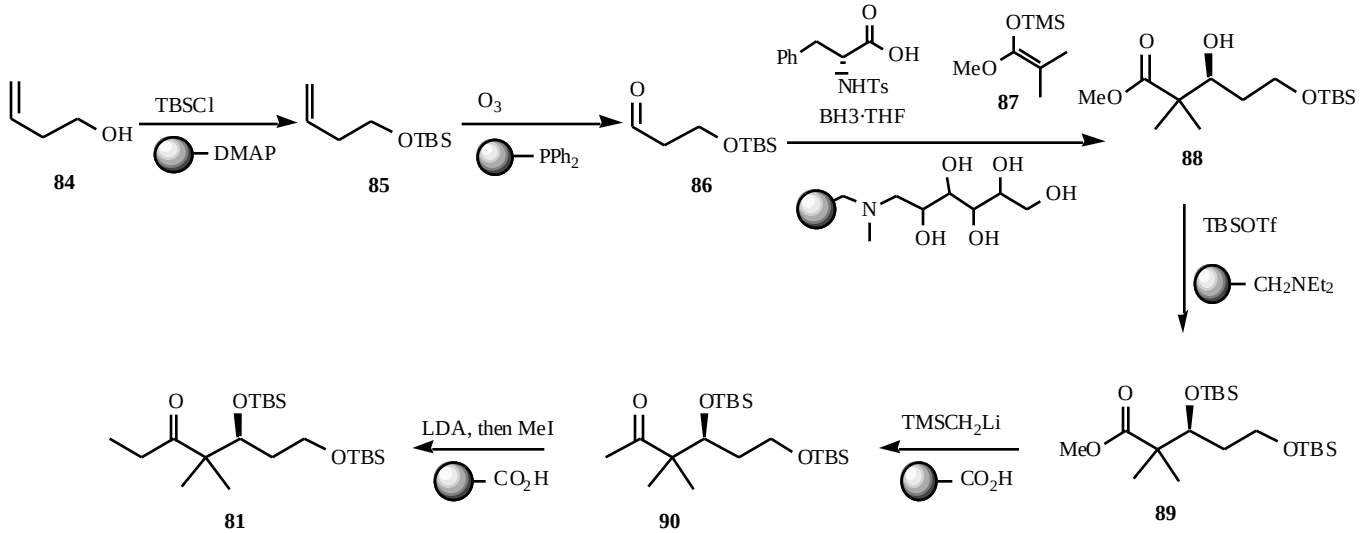
The stereoselective binding of fragment **81** to **82** by C6-C7 lithium aldol condensation was followed by a C12-C13 bond formation to incorporate fragment **83**. Subsequent ring closure by C1-C15 macrolactonization provided the natural product.

Different methods were explored for the synthesis of the three fragments. The ketone fragment **81** was synthesized by a similar route described by Mulzer and Taylor (Scheme **14**) [45]. Formation of the C3-C4 bond proceeded with concomitant introduction of the C3 stereocenter by application of the asymmetric Mukaiyama aldol reaction developed by Kiyooka.

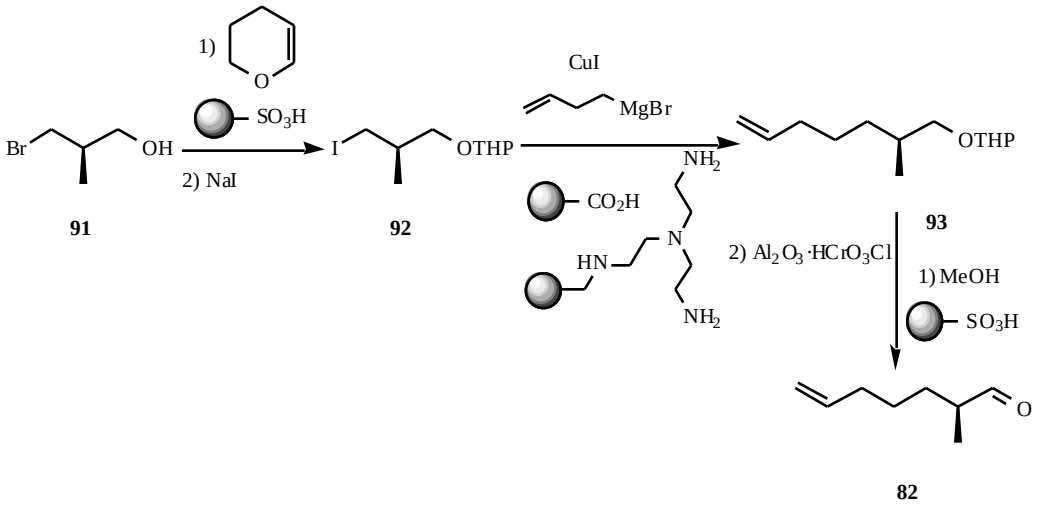
The second fragment was synthesized in five steps starting form commercially available (*R*)-(-)-3-bromo-2-methyl-1-propanol **91** (Scheme **15**).

The last fragment, **83**, was synthesized by two different strategies (Scheme 16). In this last approach the *o*-protected iodide **99** was converted to the phosphonium salt **100** by heating with polymer-supported triphenyphosphine in toluene. The resulting resin-bound phosphonium salt had a loading of 0.9 mmol $g^{-1}$.

Aldol coupling of the ketone **81** and the aldehyde **82** using lithium diisopropylamide in THF provided the anti Felkin-Anh adduct **101** in excellent diastereoselectivity, although an excess of aldehyde was needed to improve the yield (Scheme **17**). After quenching the reaction with acetic acid, diamine polymer was added to scavenge excess acid




**Scheme 14.**

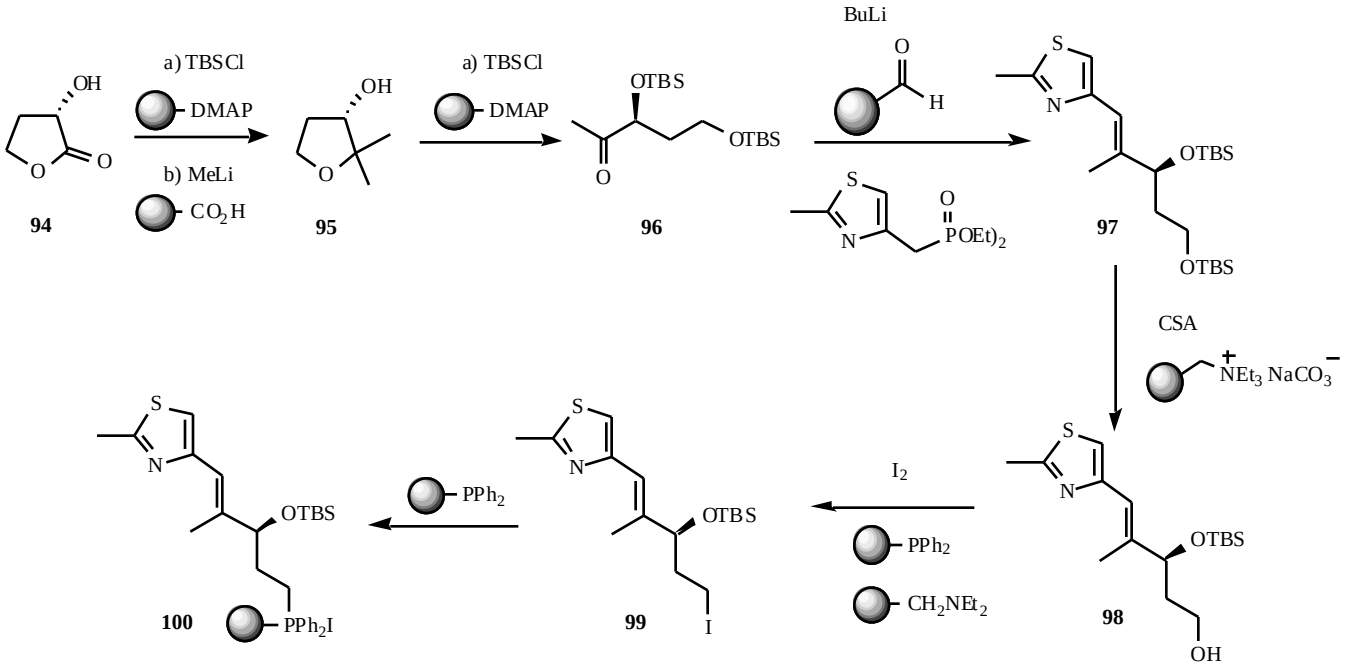


**Scheme 15.**

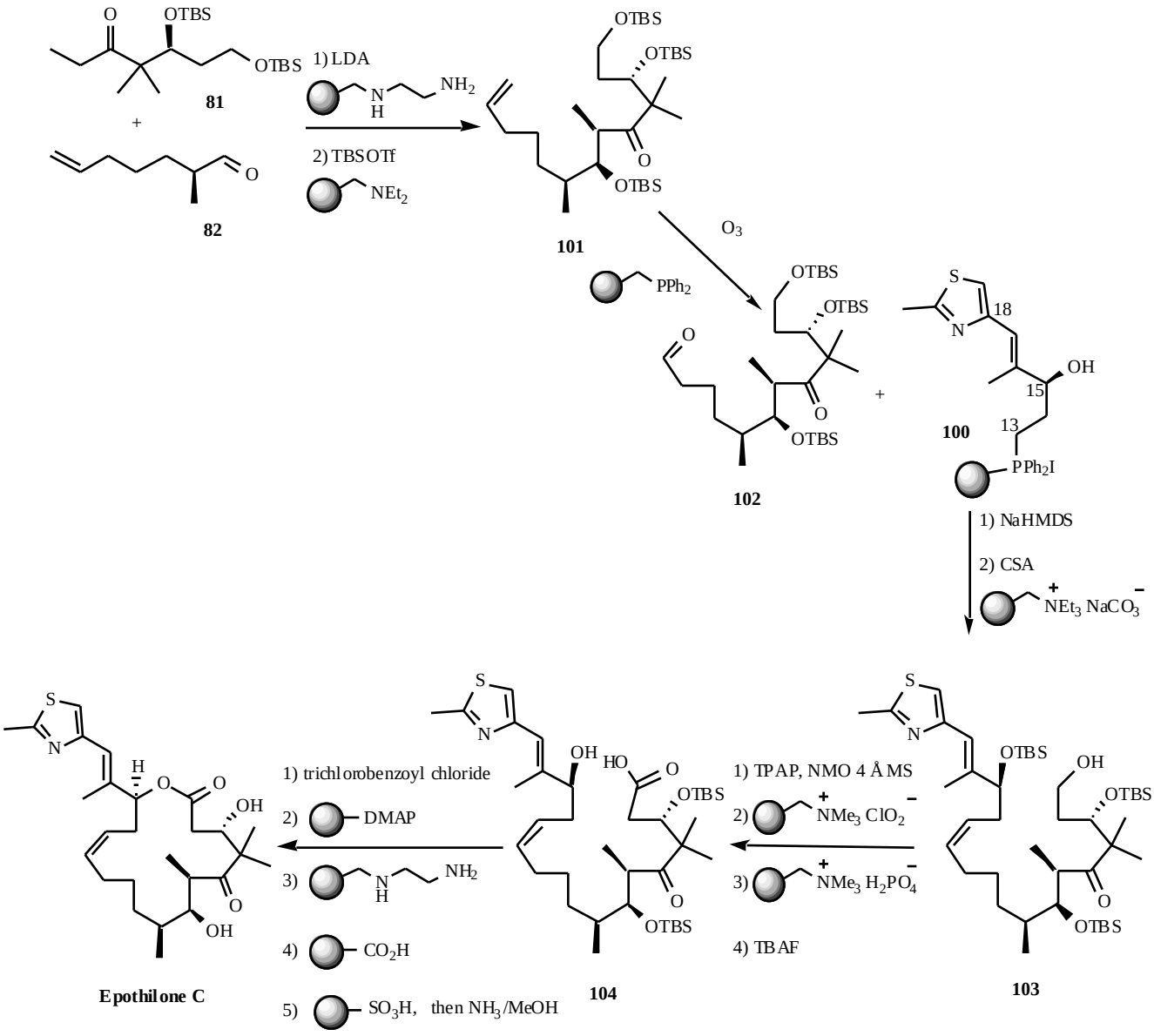
and aldehyde fragments from the crude reaction mixture. Polymer-supported triphenylphosphane was later used with ozone to obtain the terminal aldehyde needed for Wittig coupling with fragment **100**. The key step of aldehyde coupling to the ylide recovered from the resin provided the *cis* olefin exclusively. The last crucial step was the macrolactonization of linear hydroxy acid **104** using a polymer-supported DMAP under Yamaguchi conditions to provide the required 16-membered lactone [44]. Resin-bound sulfonic acid was used to remove both TBS protecting groups and to protonate the thiazole nitrogen atom for ion-exchange purification of the natural product. Following several washes, epothilone C was released from the resin by using a solution of ammonium in methanol, and subsequently purified by flash chromatography. The authors went on to compare this 29-step synthesis with the best previously published syntheses.

## CONCLUDING REMARKS

As illustrated in this review, solid-phase chemistry is well-established for the preparation of complex natural products. In addition to providing scaffolds for total syntheses, resin-bound reagents can facilitate reactivity and/or purification when used as part of solution-phase strategies. Solid-phase chemistry is also amenable to parallelization, thereby facilitating the construction of compound libraries. Many of the myriad reactions compatible with solid support (e.g., Sonogashira, Suzuki, oxidations, reductions, cycloadditions) were used in key steps of the syntheses described. Some of these synthetic strategies involve a cyclative cleavage, in which structures containing particular moieties are selectively released from the support. Although the robustness of polystyrene-based resins makes them the preferred choice for many reactions, other polymer supports have been also used. PEG-based



**Scheme 16.**




**Scheme 17.**

resins, for example, allow resin-bound reactions to be run in solution until completion, at which point the product-resin complex can be precipitated. While current methods may not be suitable for all natural product targets, the ever-expanding arsenal of chemistries performed on polymer-support will undoubtedly play a pivotal role in future syntheses of these compounds.

## ACKNOWLEDGEMENTS

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